Compliments of the Author

Report of a Case of Alcoholic Multiple Neuritis, with Autopsy

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Assistant in Pathology, Columbia University

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By J. H. LARKIN, M.D.,

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ALCOHOLIC neuritis has been the subject of so many studies that it might appear unnecessary to try to contribute anything new either to its clinical picture or its underlying pathological conditions. Leyden, Erb, Strümpell, Gudden, and others have so thoroughly covered the ground from the clinical standpoint that little can be added to their extensive studies, but in the sphere of pathology newer methods of investigation have offered an opportunity for the recording of certain cytological changes, as yet not thoroughly understood nor classified. While it is perfectly true that of late years a number of observations have been made by means of these methods, the amount of evidence, we believe, is still insufficient to permit of generalizations that might cover all cases of alcoholic neuritis. Heilbronner[2] has in recent studies exhaustively covered the field of the fibre degenerations of the peripheral nerves and of the spinal cord, and it has been the object of the present communication to confine itself to a study of the ganglionic changes observed. Such ganglionic changes have been recorded for years. Their extreme grade in some cases made their recognition comparatively easy, even when studied by the carmine or hæmatoxylin micro-chemical reactions, but their clearer analysis has obtained only since Nissl introduced his general methods. By these methods the changes have been studied by a number

[1] The writers desire here to express their thanks to Dr. O. Seibert for the privilege of reporting this case, and to Dr. T. M. Prudden for assistance and counsel.

[2] Monatsschrift f. Neurologie u. Psychiatrie, 3, 1898, p. 457 et seq.

of observers experimentally, and in the human subject. Polyneuritis due to other closely related toxic agents —tuberculosis, diphtheria, malaria, typhoid fever, beri-beri, etc., has also been carefully investigated, and the analogies to alcoholic neuritis are close.

The following case has been reported, since it presents certain features worthy of note. It is a simple, uncomplicated case, and the pathological picture, in so far as the clinical history could determine, should show the effects of a sudden acute alcoholic poisoning. Other factors which are known to be the cause of changes in the ganglion cells of the central nervous system can be excluded. This is a condition which is extremely rare among the cases reported which have come to autopsy. In the great majority of these, chronicity, accompanying renal disease, bacterial toxæmias, hyperpyrexia, or other cause of cell degenerations have been present, as revealed by a close scrutiny of the clinical histories. The work of examining these histories has been materially lessened in Gudden's tabulation of forty-eight cases and Heilbronner's careful digest of some sixty cases. No collection of the recent work on alcoholic paralysis, as revealed by the Nissl method, has as yet been attempted. Ewing[1] has given perhaps the best short *résumé*.

History of patient: Mrs. C. S——, aged thirty-five years, admitted to St. Francis' Hospital, May 13th, suffering from paralysis of both arms and legs, with slight catarrhal jaundice, gastric disturbance, and excruciating pain in arms and legs.

Past history: She has been married eight years, and has had five children, two abortions. The oldest child is seven years, the youngest one year old. All the children were normal births and are at present healthy. The patient has had the ordinary diseases of childhood, and has always been a robust and healthy woman. She has always been in the habit of using beer and wine to a moderate extent.

Present history: About one year ago she lost her mother and two brothers under peculiar circumstances. These she considers the causes of her over-indulgence in strong alcoholic drinks. Her debauches were of a periodical nature. She would drink for weeks at a time, taking no food of any account while on these sprees. At the end she would gradually "taper off"

[1] Archives of Neurology and Psycho-Pathology, 1, 1898, p 263.

and remain well, drinking no liquor in the interval. The periods between these debauches would be months. At one time she went four months without tasting liquor of any kind. Her last debauch began on March 15th (?), 1898. From that time until April 15th (two to four weeks) she drank very heavily. About April 2, 1898, she awoke one morning with a sensation of "pins and needles" in both hands and feet. This continued during the day and for about twelve days, when the sensation changed gradually to pain, slight at first, but increasing as the days went by. She was treated at home this time for rheumatic pains and sciatica. About April 15th she noticed that her skin was turning yellow and that her feet began to swell, and she became somewhat short of breath. The pains in both feet were then of a severe shooting character, while those in her hands were only moderate in degree. From this time on she was evidently growing rapidly worse, and on the advice of her physician was removed to the hospital on May 13, 1898.

On admission: The patient is well nourished. There is some œdema about the face and puffiness under the eyes. There is moderate jaundice, especially noticeable in the sclerotic of the eye. There is œdema of both extremities, with spasmodic twitching of the leg muscles. The patient's facies is one of suffering, and she complains bitterly of the pain in her arms and legs, which gives her no rest.

Physical examination: The heart apex is in the sixth interspace. The impulse is forcible, with some slight pulsation over the pericardium. The heart area of percussion is large. There is a systolic murmur of moderate intensity heard at the apex and transmitted to the left under the axilla, and heard only feebly at the back, at the spine, or the scapula. The lungs are normal. The liver extends three finger-widths below the free border of the ribs on the right side; its edge is moderately rounded. The spleen is not palpable, but on percussion seems moderately increased in size. There is nothing noticeable about the abdomen. The kidneys: The urine is 1.018 specific gravity, acid; albumin, very delicate trace with nitric-acid test; no casts. White and red blood cells are few. There is no sugar. There is some involuntary evacuation of bladder and rectum. The patient's legs are drawn up. There is marked pain, made worse on pressure

over the nerve trunks. Double drop-foot and spasmodic twitching of leg muscles are present. No evidence of atrophy of any groups can be made out on account of œdema. The tendon reflexes are lost on both sides. There is flattening of the muscles of the buttocks, with considerable pain all along the spinal column. There is double drop-wrist; the skin and tendon reflexes are abolished. The muscles of the forearm are atrophied and flabby.

The pain sense was examined by electricity, hot and cold water, and by needle. The electrical examinations were not extended. The faradic current alone was used. The current employed was so strong that a normal individual could not stand it, yet the patient never evinced the slightest discomfort. Complete analgesia to needle pricks was present. Tests with heat and cold were not successful, as the statements of the patient were not satisfactory. Reaction of degeneration was well marked in the extensors and flexors of lower limbs and forearms.

The patient continued to grow steadily worse day by day. The pain in the back, arms, and legs was excruciating, and required anodynes for relief. On May 27, 1898, the patient grew slightly delirious. The temperature was 103° F. The pulse was rapid and small. On the following day the delirium was more marked and the patient had to be restrained. On May 29th, the delirium changed to a stuporous condition. In this she remained till she died on May 31, 1898, without any marked rise in temperature.

The autopsy was made by Dr. Larkin, three hours post mortem. The body is that of a well-nourished woman. There is moderate general jaundice; no rigor mortis; no post-mortem lividity. There are several nodular tumors (sebaceous cysts), about the size of a marble, in the subcutaneous tissue of the scalp, freely movable. There is an old cicatrix over the front of the tibia at lower third, the probable seat of recent traumatisms. Both mammary glands are well developed. There is moderate subcutaneous fat tissue, which is bile stained. The muscles are dark brown in color. The abdominal cavity is yet warm. There is about a litre of bile-stained serum in the abdominal cavity. There is no evidence of peritonitis, either old or recent. The liver extends three finger-widths below the free border of ribs.

The lungs: There is no fluid in either pleural cavity.

There are no adhesions. The posterior pendent portions of both lungs are in the condition of hypostatic congestion and œdema; otherwise they are normal.

The heart: There is no fluid in the pericardium. There is moderate pericardial fat tissue. The heart weighs 60 gm. There is hypertrophy of the wall of left ventricle. The aortic valves are normal. The mitral valves are thickened along the free edge with thickening of the chordæ tendineæ; the pulmonary and tricuspid valves are normal. There is no atheroma of the aorta. The liver is congested, slightly increased in size and granular, and is in a condition of beginning mild cirrhosis. The spleen is increased in size; its pulp is dark brown; the capsule is thickened and the trabeculæ are prominent. The kidneys weigh 245 gm. They are uniformly congested and succulent, with non-adherent capsules and irregularities in the markings of the cortex, which is also slightly diminished. There are no changes in the blood-vessels. The pancreas presents no gross changes. The stomach is coated with glairy mucus; there is some congestion at the pylorus, otherwise normal. The tubes and ovaries as well as the uterus are normal. The brain and spinal cord present no observable gross anatomical lesions, the pia mater over the frontal lobes alone showing some slight œdema.

Microscopical examination: The lungs, heart, spleen, and pancreas show no microscopic change. The liver shows increase of connective tissue in Glisson's capsule; there is general congestion of central veins and capillaries. The kidneys show chronic congestion with slight increase of connective tissue between tubules; swelling of cells lining Bowman's membrane, increase of cells in and on capillary tufts; no degeneration of the epithelium lining tubule; the blood-vessels except for congestion are normal. Posterior tibial nerve: the sections show slight œdema of connective tissue and swelling of the endothelium lining the blood-vessels.

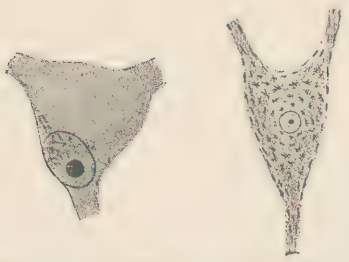
Technics: The brain and spinal cord were removed and placed in absolute alcohol within three hours of the time of the patient's death. The pia of the brain was removed and the cord was cut in sections of about 2 cm., still adhering to the dura on one side in order to *orientier* the segments. Portions of the peripheral nerves were fixed in absolute alcohol and in osmic acid.

The microscopical technic need only be summarized. After thorough fixation and hardening several weeks, portions of the spinal cord and brain were embedded in celloidin, and sections cut from 5 to 20μ in thickness. These were stained by Nissl's methylene-blue preparation and mounted in damar. Held's modification without the acetone was also employed. Delafield's hæmatoxylin and eosin were employed in some of the studies of the nucleus and for the blood-vessels. Heidenhain's iron hæmatoxylin was also employed in some instances. Von Rehm's method gave excellent pictures of neuroglia elements. The cord was studied at intervals of 1 cm. throughout its entire length. The medulla and pontine regions were also sectioned through the more important cranial nerve nuclei. Sections from the cortex were taken from a number of areas; these will be discussed under the head of the cortical findings.

Spinal-cord changes: The white matter of the spinal cord was not closely investigated. The studies of the fibre tracts by Gudden, Heilbronner, and scores of others have demonstrated very clearly the great alterations that may be found in alcoholic multiple neuritis. Degenerations are extremely common in the ascending columns, notably those of Goll and Burdach, and the relations of the process found in alcoholic neuritis to the degenerations found in tabes have been exhaustively treated by these authors.

The examination in the present instance was purposely confined to the study of the ganglion cells, and in these there was found a degeneration of very marked extent. In many of the contributions on the subject of the ganglionic changes in this affection it is apparent that a large number of the cases are not simple ones of pure alcoholic neuritis, but are instances of the occurrence of a neuritic invasion in people who have been suffering perhaps for years with some form of constitutional or exogenous toxæmia. In many of the cases examined by the newer methods the element of chronicity is also to be borne in mind, and in still others hyperpyrexia may add its complicating changes. These points of difference are taken to be of importance in the description of the lesions of this case, since it presents a clear picture of an acute lethal intoxication in a healthy adult, and therefore more closely approximates the experimental standards than most cases recently reported and studied by the newer methods.

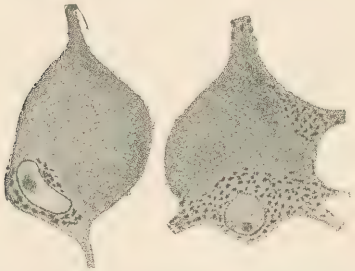
Description of the lesions in the cord: From the level of the upper cervical cord to the conus marked ganglionic degeneration was the rule. This involved not only the ganglion cells of the anterior horns, but also those in the posterior horns and throughout the dorsal cord, the columns of Clarke, and in the lumbo-sacral enlargement the nucleus of Stilling. The different levels may be considered seriatim. Manipulative artefacts were found in the cervical cord, which, to a certain extent, confused the picture, yet the ganglion cells throughout this region could be seen to be in various stages of chromatolysis. A careful count of the ganglion cells in the various levels from the seventh or eighth cervical downward is here appended, with the number of normal or approximately normal cells found therein. From the first or second to the seventh or eighth cervical there were on the average about ten per cent. normal cells in the anterior horns; fully ninety per cent. were degenerated.



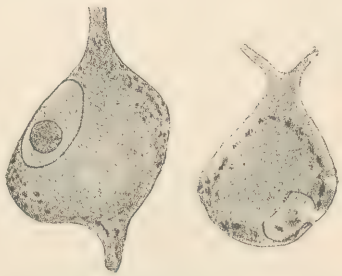
FIGS. 1 AND 2.—Cells from Anterior Horn. Fourth cervical segment showing, in 2, beginning chromatolysis; 1, more advanced stage.

	Anterior Horns. No. of Cells Present.		Anterior Horns. Normal Cells.		Column of Clarke. No. of Cells Present.		Column of Clarke. Normal Cells.	
	Right Side.	Left Side.	Right Side.	Left Side.	Right Side.	Left Side.	Right Side.	Left Side.
1st dorsal ..	15	9	3	0	16	14	2	0
2d " ..	12, 13	10, 11	5	1, 2	10	5–6	1–2	0
4th " ..	18	8	0	0	10	8	1	0
6th " ..	15	8	1	1	13	10	1–2	0
8th " ..	10–12	10	0	0	16–18	17	0	0
10th " ..	7–8	6–7	0	1–2	20	13	1–2	1–2
11th " ..	10–12	10–15	5–6	1–2	15	12–13	1–2	1–2
12th " ..	6–7	6–7	1–2	1–2	20	20	3–4	4–5
1st lumbar ..	10–12	6–7	1–2	3–4	20	21	2–3	5–6
2d " ..	12–15	13–15	6–8	3–4	7–8	6–7	3–4	1–2
3d " ..	45	30	4–5	1–2	1–2	3–4	0	0
4th " ..	40–50	35	0	0	5	4	0	0
1st and 2d sacral	40–50	35–40	5–6	4–5	1–2	1–2	0	0
4th sacral ...	60–70	50–60	6–7	5–6	0	0	0	0

The above table indicates the extent of the cellular degeneration. As to its character the following general remarks may be made: Nearly every described grade of chromatolysis was observed—peripheral, central, perinuclear, etc.—but the predominant type was the well-known central chromatolysis so characteristic of axonal degenerations. In a great many of the cells, perhaps fifty per cent. of them, from the fourth to the tenth dorsal region and in the lumbar enlargement, the chromatolysis had advanced to the extreme grade of complete loss of stainable substance, reticular or cytoplasmic, and even to complete cell destruction. Eccentricity of the nucleus was a predominant factor; for the plane of the section, it was present in at least thirty per cent. of the cells; sections cut in different planes would probably show it to be more universal. No relationship between the eccentric position of the nucleus and the principal dendrites or axis-cylinder process could be shown because of the practical impossibility of seeing the cell and all its parts, even in a series of sections. As far as could be ascertained, the nucleus appeared to be at the farther extremity of the cell, as contrasted with the site of origin of the axis-cylinder process, but this is more a matter of conjecture than proof.



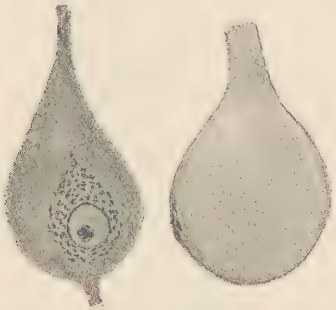
FIGS. 3 AND 4.—Degenerative Change in Upper Dorsal Region. Third segment, left side; central and peripheral chromatolysis, nuclear eccentricity and chromophilia.



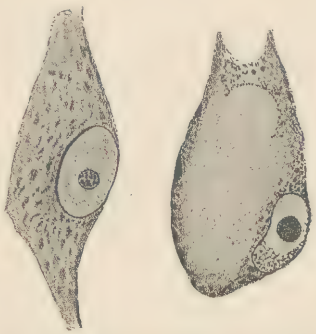
FIGS. 5 AND 6.—From Columns of Clarke. Upper dorsal segments, left side, showing different chromatolytic changes.

The greater involvement of the cells of the left side of the cord is noteworthy, the decrease in their

number signifying actual cell destruction, and in those remaining the chromatolysis was more extensive. Changes in the cyto-reticulum of the nucleus were manifest in most of the levels, though this part of the cell structure seemed more resistant than the structures of the cytoplasm. No special constant nucleolar variations could be posited; fragmentation occurred, but seemed capricious, occurring in fairly normal cells and in cells completely destroyed; well-marked nucleoli were abundant in badly degenerated cells. The absence of nuclei was probable in a number of cells, this did not occur so often as would appear from a study of any one plane, since the section just above or just below might contain the nucleus. This consideration leads the writers to maintain that for the general study of the degenerate processes in nerve cells it is wiser to use sections which are cut thicker than is frequently advised. Ganglion cells are frequently from 60–90μ in diameter, and sections of 5–10μ, which are said to be desirable, do not permit a correct interpretation of the structure unless cut in series and so studied. We prefer sections about 20μ in thickness for average work. Specially thin sections certainly are of service for the finer cytological detail of the cyto-reticulum, but for the general study of the chromatolytic process we

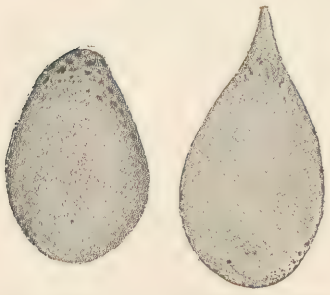


FIGS. 7 AND 8.—Degeneration of Anterior Horn Cells, at second lumbar segment, right and left sides. 7, Peripheral chromatolysis, nuclear chromophilia; 8, complete chromatolysis, nucleus disappeared, cyto-reticulum still present (in specimen).



FIGS. 9 AND 10.—Upper Sacral Segments, anterior horns showing milder grades of chromatolysis. Fig. 9 is almost normal save for slight fragmentation of granules and eccentricity of nucleus; Fig. 10 shows slight central chromatolysis.

believe them to be less serviceable. This is especially true in the case of the cells of Clarke's columns. In the present case it would appear that there was a marked degeneration of practically the entire column of Clarke, yet the structure of the cells of Clarke's column, we think, is different from those of the anterior horn in several cytological details; and it undoubtedly occurs that in these cells very thin sections give pictures of what appears to be marked central chromatolysis with centric nuclei and a fringe of cross sections of chromophilous bodies on the periphery of the section. Believing as we do that the interior of the body of the cells of the column of Clarke has fewer formed chromophilous bodies than the periphery, it would follow that such a picture is readily misinterpreted. When the granules at the periphery have entirely disappeared and the nucleus is eccentric, the interpretation is beyond cavil, but there are, we believe, grounds for questioning the observations made on too thin sections in the cells of the columns of Clarke.



FIGS. 11 AND 12. — Columns of Clarke. Eighth dorsal segment, left side, complete cellular degeneration.

Portions of the brain were taken from the following areas (their exact location is represented in the subjoined diagram): 1, superior frontal; 2, mid-frontal; 3, inferior frontal, just in front of the pre-Sylvian fissure; 4, operculum, just behind the pre-Sylvian fissure; 5, at the base of the central fissure, anterior central convolution; 6, anterior central convolution about the junction of the middle and lower third; 7, anterior central convolution, junction of middle and upper third; 8, top of anterior central convolution, including part of the paracentral lobule; 9, post-central convolution; 10, middle superior parietal; 11, superior temporal; 12, mid-temporal; 13, inferior temporal; 14, inferior parietal; 15, cerebellum.

These were treated by the same technical methods as outlined for the cord.

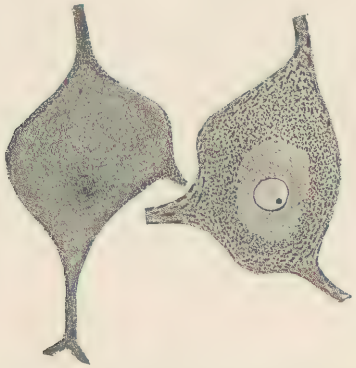
1. Superior frontal convolution: The large and me-

dium-sized ganglion cells throughout fairly normal; sub-pycnomorph, pigment prominent; many nuclei eccentric, though in these cells where the nucleus makes such a large part of the cellular mass, little weight is to be placed upon such eccentricity. The blood-vessels were not materially altered.

2. Mid-frontal convolutions: The ganglion cells were normal in this region as far as could be determined, though many had eccentric nuclei.

3. Preopercular convolutions: No appreciable lesions were observed.

4. Operculum: In the large and medium-sized ganglion cells the cytoplasm was finely granular. Pigment was present in many, and in a few of the cells the



FIGS. 13 AND 14.—Cells from Nucleus of Stilling. Lumbar and sacral region, showing, 13, complete chromatolysis; 14, beginning perinuclear chromatolysis.

nucleus was eccentric. The blood-vessels were not affected.

5. Base of the anterior central convolution: The large and medium-sized ganglion cells showed little trace of any stichochrome structure. The cytoplasm was finely granular; many of the nuclei were eccentric.

6. Anterior central convolution, junction of lower and middle third: The medium and large sized ganglion cells were markedly bleached. The typical stichochrome arrangement of the chromophilous bodies was absent, fine granules taking their place. The majority of the nuclei were centric. The dendrites were paler than in the normal condition and showed no stichochromes. Advanced grades of chromatolysis, similar to that found in the cord, was found in a few of the large ganglion cells of this region. The blood-

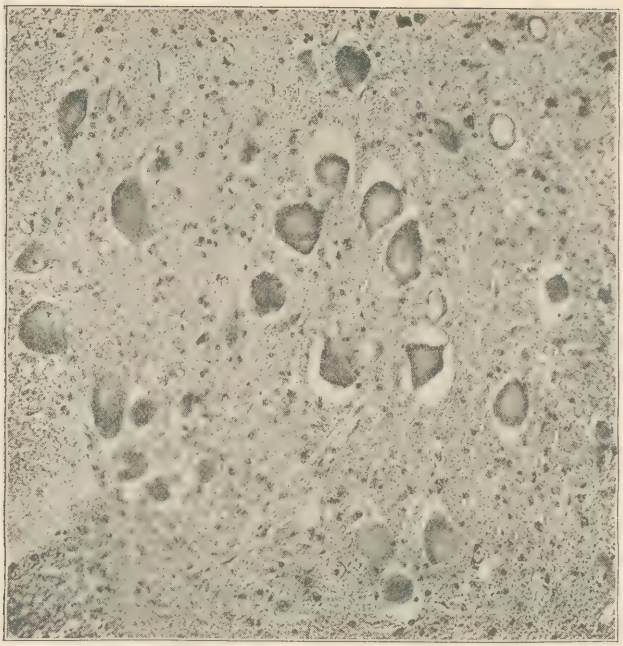


FIG. 15.—Column of Clarke. Cross section at eighth dorsal segment, left side, showing various grades of chromatolysis. (Photomicrograph by Dr. Leeming.)

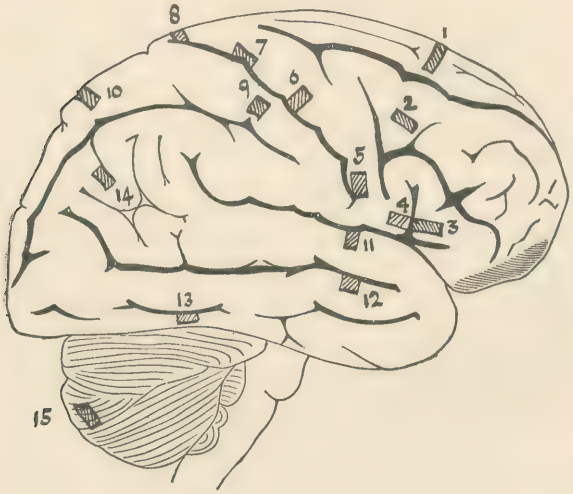


FIG. 16.—Diagram of Brain, showing position from which the portions examined were taken.

vessels were not markedly altered, though moderately dilated.

7. Anterior central convolution, junction of upper and middle third, was not so markedly affected as the section 6. Stichochrome structures were here apparent and the nuclei were more centric. Many of the cells, however, had nothing but a fine granular cytoplasm. Pigment was rare. The blood-vessels were normal.

8. Top of the anterior central convolution, including a part of the paracentral lobule. Many of the cells in this region showed partial degenerative changes, especially those in the paracentral lobule. Many had eccentric nuclei, and the reticulum of the cytoplasm was obscured. But few of the ganglion cells had retained any stichochrome arrangement of their chromatic substances.

9. Post-central convolution, middle third: The cells in this region were not materially altered.

10. Superior parietal convolution: The medium and large sized ganglion cells of this region were noticeable by reason of a large amount of pigment. Beyond a certain amount of granulation of the cytoplasm they appeared normal. There were no nuclear changes observed.

11. Superior temporal region: There were no marked structural changes in this region. A slight grade of granulation of the cytoplasm alone was observed.

12. Mid-temporal convolution: Few structural modifications were found in this region.

13. Inferior temporal convolution: Mild degenerative changes were found in the sections from this region. The dendrites were not prominent and the cyto-reticulum was obscured. The reticulum of the nucleus was normal.

14. Inferior parietal convolution: This seemed normal.

15. Cerebellum: The Purkinjé cells were pale throughout. In nearly all of them there were some small chromophilous bodies clustered near the nucleus. The dendrites were mostly colorless and the nuclei were in a stage of chromatophobia. There was no marked eccentricity of the nuclei of the Purkinjé cell. The nucleoli were regular. The blood-vessels of the cerebellum seemed normal.

Résumé of changes in the cortex: There were, therefore, distinct degenerative lesions irregularly dis-

tributed throughout the cortex of the brain. These consisted for the most part of the following: In the cortical stichochrome cells of the motor cortex there was a disappearance of these bodies, an irregularity in the position of the nucleus, and qualitative variations in the staining portions of the cytoplasm. The archyostichochrome cells in many cases had lost the charac-

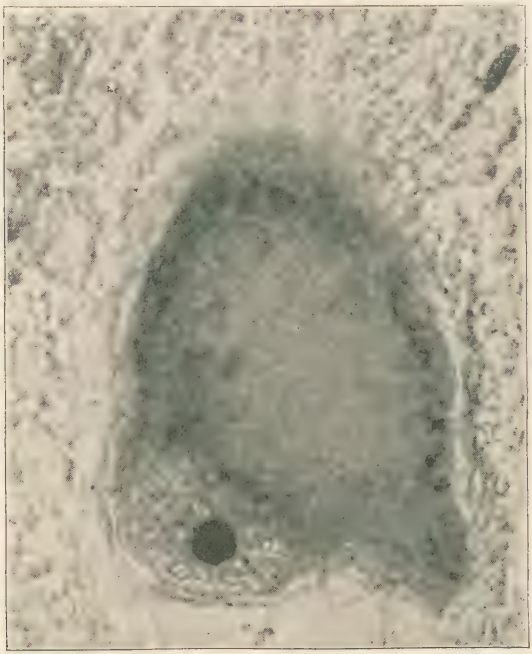


FIG. 17.—Cell from Anterior Horn, fifth cervical segment; central chromatolysis, eccentric nucleus, central destruction of reticulum. (Photomicrograph by Dr. Leaming.)

teristic arrangement of their reticulum, and the cytoplasm showed a distinctly granular structure. Peripheral chromatolysis was present in the Purkinjé cells of the cerebellum.

In any discussion of the lesions produced by the alcoholic poison, the *rationale* of the process, in so far as it is understood, should be borne in mind. It would seem that two distinct series of changes might be going on simultaneously in multiple neuritis—one similar to that produced by a degeneration or a cutting-off of the axis-cylinder process, and the other a direct poisoning of the ganglion cell.

Under experimental conditions the changes produced by the former process are fairly well understood, but the cytological variations, which might be due to the direct poisoning, may not be so readily correlated. Vas, Dehio, Berkley, and Stewart have given us contributions to this latter question; with the former ques-

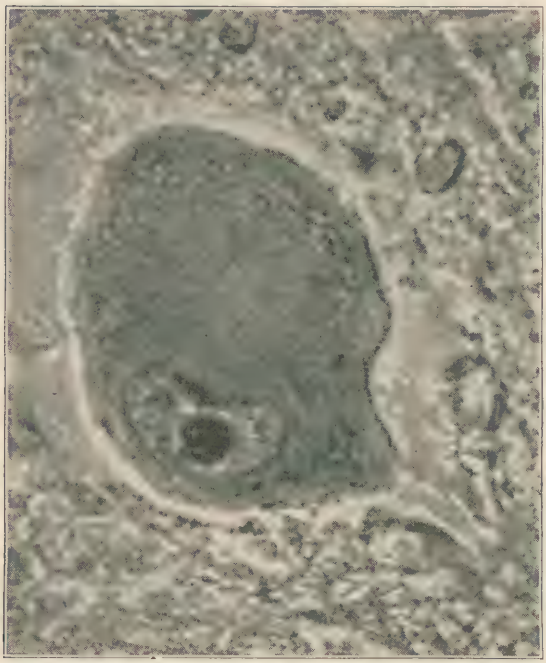


FIG. 18.—Cell from Column of Clarke. Left side, tenth dorsal segment, showing central chromatolysis; eccentric nucleus. (Photomicrograph by Dr. Leaming.)

tion a host of observers have busied themselves. Marinesco has compressed the final matter in a nutshell, thus: "After the section of a motor nerve or of a sensory nerve, in from five to six days there are certain positive lesions in the ganglionic centres of these nerves, as shown by Nissl's method of examination. These, as given in *résumé*, are: (1) A partial dissolution. Disappearance of the chromophilous elements of the nerve cells. This process may affect the entire cell body. The nucleus, more or less altered, is usually found at the periphery of the cell body. (2)

When the lesion has affected the entire cytoplasm of the cell, it presents a homogeneous aspect. (3) A process of restoration may take place as the regeneration of the sectioned nerve takes place."

But while this presents a picture of the end results, it tells very little of the natural history of the process, if it has a definite cycle. Ewing believes from a wide experience, in by far the best presentation of the whole subject of ganglionic changes thus far given to technical pathological literature, that the minute variations in the process of the parenchymatous degenerations present an almost endless variety of possibilities. "The minute lesions seem to differ in every case, and the range of minor peculiarities is practically limitless. Especially in the advanced stages of acute and chronic degeneration the aspect of the cells may be so heterogeneous that classification of the lesions is impossible."

The reported cases of fatal alcoholic multiple neuritis, examined by the newer methods, have not been very numerous, nor does there seem to be a consensus of opinion with reference to the central lesions. In this form of neuritis the absence of changes is reported by Tooth, Achard and Soupault, Dejerine, and others. The first two, though coming within the "Nissl epoch," do not appear to have been examined by his methods, but in them attention was paid to the search for central lesions.

In Tooth's[1] case, which clinically ran a typical course, there was extreme degeneration of the peripheral nerves, but no central lesions were found. The cytological investigation was by means of the older methods for the most part.

Achard and Soupault[2] report two cases—one negative and one positive. The first occurred in a man, aged twenty-eight years, first received in the hospital in a condition of acute delirium after a two months' steady indulgence in absinthe. Three weeks previous to entrance he commenced to have the initial paræsthesiæ and pain of the neuritic process. He had

[1] Tooth, H. H.: "Degeneration of the Nerves in Alcoholism." Transactions of the Pathological Society, London, 1894.

[2] Achard, Ch., et Soupault, M.: "Deux cas de paralysie alcoölique." Arch. de méd. exp. et d'anatomie path., 5, 1893, p. 359.

been delirious two days previous to his entrance. His delirium cleared up in a few days, and the peripheral-nerve involvement was then manifest. He had marked paralysis of the limbs of the lower extremity, the extensors in particular, with foot-drop and also extensor paralysis of the arms and forearm. The patient developed a high temperature and died of syncope with evening temperature of 39.2° C. (102.5° F.). The autopsy showed meningeal congestion. The cord seemed normal. There was congestion of all of the viscera and heart muscle (myocardial fragmentation). The cells of the anterior horns were normal; some in the cervical region were tumefied and transparent. There were no changes in the medulla. The examination of the nerves showed some degeneration, especially in the median, cubital, and right radial nerves. The changes in the heart, kidney, and liver were of a parenchymatous type.

The case of Dejerine and Thomas is of more interest. These authors[1] report some observations made upon a case of a cook, forty-eight years of age, who had alcoholic paralysis of the lower extremities, with atrophy and talipes equinus. There was hyperæsthesia of the skin and of the muscles, and abolition of the patellar reflexes. On autopsy there were found marked lesions of the cutaneous nerves of the lower extremities. There was integrity of the anterior and posterior roots, gray matter, and ganglion cells. It is of interest to note in this case that the patient was in process of recovery. There had been a complete paralysis of the upper extremities, but this had disappeared and the lower limbs were regaining their power somewhat. The cutaneous nerves were examined in osmic acid, and the cord was examined by both the Nissl and Marchi methods. The authors believe that the absence of the ganglion-cell changes may have been due to the fact that the peripheral nerves were re-establishing their function, though at the time of death paralysis was still present. Moreover, they show that chromatolysis should not be too rigidly interpreted, since it may be found in cases like these, or in cases, as Jacottet[1] has shown, in which there was apparently

[1] Dejerine, J., et Thomas, A.: "Sur l'absence d'altération des cellules nerveuses de la moëlle épinière dans un cas de paralysie alcoölique en voie d'amélioration." Comptes rendus de la Soc. de Biologie, May 1, 1897.

[2] Thése de Lausanne. 1897.

no impairment of function, yet marked cellular changes were present. Thus chromatolysis links itself with other parenchymatous cell changes, and its significance is great, yet not pathognomonic of any single type of lesion.

Soukhanoff [1] has reported a positive and a negative case. His negative observations were in the case of a young man of twenty-one, who for some years had been a hard drinker. He had a poor family history and suffered from delirium tremens, so that his case might be considered one of multiple alcoholic intoxication, extending over a period of some years. At the autopsy it was shown that he had a marked chronic leptomeningitis; the cerebral substance was œdematous and the ventricles were markedly dilated. There was sclerosis of the arteries of the base of the brain. There was a purulent infection of the pleural sac and tuberculous cavity formation in the right lung. Thus this case is not an uncomplicated one, and the changes in the nervous tissue may be due in part to the alcoholic poison and in part to the action of toxins. The peripheral nerves stained with osmic acid showed the characteristic picture of degeneration. The spinal cord in the lumbar region treated by Marchi's method showed a marked involvement of the posterior columns. There were degenerated fibres interspersed with healthy ones. Some few degenerated fibres were found in the anterior and lateral columns, and in the anterior commissure there were also degenerations. The cervical region showed a most marked degeneration in the column of Goll. Examined by the method of Nissl and by carmine, the author states that notwithstanding the extensive fibre degenerations there were no appreciable lesions noted in the ganglion cells. The changes in the medulla were of the same type. There were a few degenerated fibres going to and from the hypoglossal, facial, abducens, and oculo-motorius nuclei. Examination of the brain was negative by Marchi's method.

From a careful reading of the histories of these cases as reported, the evidence is not sufficient, we believe, to exclude the possibility of there being some cytological alterations. In the less marked cases, as those of Dejerine and Thomas, the absence of grave lesions might be expected from what we now know of repair

[1] Soukhanoff, S.: "Contribution à l'étude des changements du système nerveux centrale dans la polynévrite." Arch. de Neurologie, 1896, p. 177.

in ganglion cells, and in the more positive case of Soukhanoff it is not evident that a rigid examination was made throughout the cord, since more attention was paid to the fibre degenerations and only sections here and there were taken for the Nissl technique, a procedure which is only too apt to cause misleading conclusions.

The positive cases are comparatively numerous. We here report a number of them in which lesions similar, in part, to those found by the writers were present. Ballet and Dutil's[1] case is of interest in that it shows most of the lesions observed by us, and yet, so far as these observers were able to determine, no direct toxic agent could be found. These authors report the case of a man, aged forty-four years, who, without any ascertainable infectious or toxic cause, developed at the age of forty-four years all the symptoms of a multiple neuritis. The examination of his peripheral nerves showed the typical lesions of neuritis. There were a number of degenerated fibres in the anterior roots. The posterior roots were healthy. The most marked alterations, however, were found in the cells of the anterior horns. In a number of these there was absence of the chromophilous granules, the cytoplasm had become homogeneous and turgid, and in some of the cells the nuclei had vanished, the cells had become globular, and the prolongations had disappeared. Changes in the nuclei were also evident; the nuclear mass was irregular and even star-shaped in some of the affected cells. The peripheral position of the nuclei was evident in many of the diseased cells. The *resume* of the authors' contribution is as follows:

1. We have been able to show that in a case which presents the clinical picture of an idiopathic polyneuritis, there were lesions of the nerve trunks, of the anterior roots, and marked alterations in the ganglion cells of the anterior horns.

2. When one desires to examine for spinal cell changes in cases similar to this, it is necessary to use other cytological methods of examination than picrocarmine; such as the method of Nissl, or, if the nucleus is to be studied, hæmatoxylin.

3. It does not suffice to affirm that the polyneuritis has been secondary to alterations in the spinal cord,

[1] Ballet, M. G., et Dutil, A.: "Sur un cas de polynévrite avec lésions médullaires." Soc. méd. des Hôpitaux, 12, 1895, p. 818.

since the poliomyelitis could be secondary to the peripheral nerve lesions.

4. The arguments which are of value in favor of the medullary origin of the polyneuritis are of another kind.

The second case[1] occurred in a woman, twenty-five years of age. She was admitted to the Salpétrière following a slight convulsive attack. She had been drinking for some time, but presented a very irregular history. A month after her admission the symptoms of the neuritis developed and continued up to the time of her death, which occurred three months after the first symptoms. Phthisis was a complicating factor. Microscopical examination of the medulla showed some nuclear degeneration at the region of the olivary nucleus. The spinal cord showed sclerosis of the columns of Goll and of the lateral columns. The cells of the anterior horns were remarkably degenerated. In certain groups the cells were normal; in others, changes were profound. Normal and diseased cells were intermingled in places without any regularity. The changes for the most part were of interest only in the variation of contour, loss of prolongations, changes in colorability of the nucleus, and its dislocation to the periphery of the cell. Sometimes there was complete loss of the nucleus. These changes were noted in the cervical, dorsal, and lumbar regions, the cell changes in the dorsal region being extreme. Marked degeneration of the nerves was noted, including that in the pneumogastric.

Marinesco[2] reports a case of polyneuritis with grave central changes, but viewed from our point of view it has little bearing save upon the general peripheral pathological findings in cases of this character. The case was one lasting over two years, in an old rheumatic patient who had early in 1892 paralysis and atrophy of the muscles following an attack of acute articular rheumatism. He died in 1894. The cell lesions were marked.

See *Comptes rendus*, 1896, p. 467, for another case in contradistinction to the case observed by Dejerine and Thomas, with no cytological changes. These same authors published formerly a marked case, illustrating

[1] Achard and Soupault: *Loc. cit.*

[2] Marinesco, M. G.: "Les polynévrites en rapport avec la théorie des neurones." Comptes rend. de la Soc. de Biol., 2. 1895, p. 765.

most of the phases of the chromatolytic process.[1] In this case incontestable lesions existed in great numbers in the cells. These lesions were not equally distributed throughout the whole cord. They predominated markedly at the level of the lumbo-sacral enlargement. They diminished in the posterior inferior portion of the cervical enlargement and were hardly appreciable in the upper cervical roots. They showed further a certain parallelism between the cell lesions and the changes of the peripheral nerves. These lesions were essentially polymorphous. Beginning in one stage the cell appeared swollen, often to a considerable degree. Instead of measuring 60μ some reached 85 to 90μ. This increase of the volume was constant in all the portions of the cells, which tended to become more and more spherical; at the same time the protoplasm underwent profound modifications. It took on a general blue tint, often more marked at the middle of the perinuclear zone. The chromatic substance was represented here and there by a few striations. The plaques became finely granular. These diverse cytoplasmic alterations did not appear to them to begin by preference in the region of the nucleus. They did not seem to follow any clearly definable law. In the second stage the volume of the cells diminished; its protoplasmic mass especially staining less and less intensely. The nucleus with its nuclear membrane was made out with difficulty. It underwent a more or less considerable displacement. Finally in the last stage, which is more rarely reached, the cell body, very pale throughout, does not present any protoplasmic prolongations. The chromatic elements are reduced to minute granules scattered here and there. The nucleus is located at the periphery; its substance is feebly tinted; its membrane is often destroyed. These cell lesions having been already described in the more extended works of the pathological histology of alcoholic polyneuritis, we desire in our communication especially to call attention to their polymorphism and to their constant existence when the disease is at its greatest height.

Soukhanoff[2] reports a case of multiple neuritis of

[1] Dejerine and Thomas: Soc. de Biologie.

[2] Soukhanoff, S.: "Sur la histologie pathologique de la polynévrite dans ses rapports avec les lésions de la cellule nerveuse." Nouvelle Iconographie de la Salpétrière, 10, 1897, p. 347.

probable alcoholic origin, in which both the methods of Nissl and of Marchi were used in the examination of the central nervous system. In the ganglion cells of the anterior horns there was marked central chromatolysis, and the nucleus was driven to an eccentric position. In a few cases the nucleus was centric with some perinuclear chromophilous substance, but about this the chromatolysis was marked. The author interprets the cell changes in two ways: In those cells with centric nuclei and with perinuclear chromatolysis the changes are probably primary, whereas in other cells the lesions are probably secondary to degeneration in the nerve fibres.

This position is, we believe, difficult to maintain.

Ewing[1] in his recent monograph reports a case with typical course, in which paralysis had been present for about two months. He found that, throughout the lumbar cord, the anterior horn cells showed all the changes described as following the section of nerve trunks. Nearly every cell showed marked central or complete chromatolysis with eccentricity of the nucleus. Many of these cells had passed beyond this stage and were entirely lacking in normal characters, containing no traces of chromatic substance, and both cell body and nucleus appearing greatly shrunken. The earlier stages of the same lesions were found in the cervical cord. Throughout the cranial nerve nuclei the majority of the cells showed central or complete chromatolysis, with eccentricity or protrusion of nuclei. Many of the cells in some nuclei, however, appeared quite normal. The nucleus *x* and nucleus ambiguus were extensively altered. The cells of the cortex and cerebellum showed only slight fading of chromatic bodies or appeared quite normal.

Heilbronner[2] has given us one of the most careful and extended studies of multiple alcoholic neuritis of recent years. In limiting his investigations more particularly to observations of the fibre and muscle pathology, his work is of secondary interest when viewed from the present general point of view of the paper, but the suggestive results obtained by his painstaking application of Marchi's method are of

[1] Ewing, J.: "Studies on Ganglion Cells." Archives of Neurology and Psycho-Pathology, vol. i., 1898. pp. 263–440.

[2] Heilbronner, K.: "Rückenmarksveränderungen bei multipler Neuritis der Trinker." Monatsschrift f. Psychiatrie u. Neurologie, 3, 1898, p. 457; 4, 1898, pp. 1–81.

primary importance and demand a more careful analysis than can be here entered into. His results, as "zusammengefasst" by himself in his four cases, are about as follows:

1. Degeneration of the anterior horns, which in Cases I. and II. showed a marked preponderance in the lumbar cord over that found in the cervical cord, while in his Cases III. and IV. the lumbar cord was affected in a minor degree compared with the involvement of the cervical cord. The dorsal cord showed but little degeneration. In those cases in which degeneration of the anterior horns was marked, a degeneration of the fibres in the anterior horn was also appreciable, and there was an involvement of the fibres of the anterior commissure.

2. There is also a degeneration in the posterior horns, involving different areas in the cases studied; in I., the cervical more than the lumbar; in II., both alike; and in III. and IV., the lumbar cord was affected the most.

3. A fresh acute ascending degeneration in the posterior columns, which in the different cases affected the columns of Goll and Burdach in different fashion. This case showed markedly greater degeneration in the columns of Burdach in the cervical region. In Case II. there was an equal degeneration in both cervical and lumbar regions of the columns of Goll, while in Cases III. and IV. the degeneration was confined almost exclusively to Goll's columns and the lumbar posterior roots.

4. Case IV. also showed a degeneration in the crossed pyramidal tracts in addition to this degeneration of the posterior columns and the posterior roots.

One fact is brought out in relation to the similarity of posterior-column degeneration to those of tabes, in that in three cases, as studied by the Marchi methods, there is no constant pathological picture, although the clinical pictures might appear identical, and that in these cases the author notes that the lesions do not exist in every root area but are found here and there, sometimes skipping a segment or segments. In this peculiar distribution of the degenerated areas is to be found one of the cardinal points of difference in the two diseases from a pathological point of view. It is possibly due to this fact also that the case of Soukanhoff gave him no positive lesions.

The lesions that Heilbronner describes as occurring

in the ganglion cells, studied by the Nissl method, in one of his cases which presented the typical clinical picture and ended fatally without hyperpyrexia or other abnormal feature, are held by him to fall into two classes. The more common one was characterized by a minute disintegration of the chromatic bodies, at first about the nucleus, then about the periphery, without any variation in the nucleus; this latter, however, in the later stages would become eccentric. In a few cases vacuoles were to be found in otherwise normal cells. These he holds to be essentially different types of lesion, although he does not characterize them with reference to their causation.

The correlation of the structural changes found in this case with those induced by experimental alcohol poisoning has not proven entirely satisfactory. The earlier writers Vas and Dehio give us some interesting findings. Vas, by chronic alcohol poisoning, induced severe grades of malnutrition, which in turn, as he interpreted the lesions, produced a condition of general swelling and central chromatolysis. The findings of Dehio were more interesting with reference to the changes found in the cells of Purkinjé. In these mild grades of chromatolysis were observed. The fine chromatin bodies were largely replaced by finer granules. Stewart confirmed many of the results of Dehio. Berkley made some extended studies on acute and chronic alcoholism in rabbits. In his series of chronic poisonings alcohol was administered for almost a year in daily doses of from 5 to 8 c.c. The changes in the capillaries are reported upon, the walls of many of them being irregularly shrunken, the vascular wall nuclei being swollen and more readily stainable. In the cerebral cortex the somatochrome cells show alterations mainly in the nucleolus; here, in place of the smoothly appearing nucleolus in or near the centre of the nucleus, it appears roughened, spongy, or even with elongated projections from the surface. Not only is the nucleolus roughened, but it is also considerably enlarged, occupying from an eighth to a sixth of the interior of the nucleus, its projections extending to the periphery of the circle. Around these nucleolar figures is grouped a small amount of nuclear dust particles resembling an irregular circle, but the remaining portions of the nucleus are free from the presence of molecular particles. In the nucleus there is a decided tendency to take up

more of the aniline stain. So marked does this tendency become at times that the contents are rendered indistinct and the cell body is much less refractile than normally.

In a second rabbit similar changes are noted in the blood-vessels. All of the nerve cells take up a larger quantity of the aniline dye than usual. The chromophilous granules in the cytoplasm are not so distinct; the nuclei stain a deeper hue than normally. In his series of acute alcohol poisoning of three rabbits large doses were given until a certain tolerance was established; then the doses were increased suddenly until death resulted. The Nissl method of investigation showed few definite alterations save in a few cells located in the immediate neighborhood of clogged vessels. Here the cellular protoplasm did not show its stichochrome structure; it appeared uniformly and fully granular, and besides did not take up so much of the dye as other more normal cells. In these individual cell bodies there is beginning swelling of the nucleoli, and they appear slightly roughened. The nuclear dust has not aggregated into clumps and become adherent to the nucleolus, as in some of the chronic cases of the first study. In the areas where the disturbance of the circulation has been less well defined, changes in the protoplasm and nuclei of the cells are not very positive. The stichochrome particles of the protoplasm are seen somewhat less clearly than normal, and the protoplasm as an entirety shows greater receptivity to the aniline stain than is customarily seen, or, better, they will not bleach out with the same facility that they ordinarily do. The nucleus and nucleolus appear to be strictly natural. The striated appearance of the thicker dendrites near the cell body is always seen.

These results, if they occurred in the present case, were certainly overshadowed by the changes probably induced by the peripheral disease, for, beyond some slight nucleolar fragmentation, the lesions observed were not characteristic of the findings as given by these experimental studies. In man the changes found in delirium tremens have been very various. Some observers report almost no changes at all, while others find extreme grades of cell degeneration. Perhaps none are more pronounced than those observed by Ewing.[1] He reports two cases, both of which were

[1] Ewing, J.: "Studies on Ganglion Cells." Archives of Neurology and Psycho-Pathology, vol. i., 1898, pp. 263–440.

fatal in a condition of delirium tremens. There was some hyperpyrexia just before death, 104°–105° F. One case was complicated by acute kidney disease, the other by slight catarrhal pneumonia. These cases present a clear picture of the alcoholic poisoning. The spinal, medullary, and cortical stichochromes presented the lesion of extreme chromatolysis. No normal cells were seen anywhere, and in only a few were there any traces of the peripheral ring of chromatic bodies, often seen when the disintegrating process begins about the nucleus. In many cells, especially in the cranial nuclei, the lesions had advanced far beyond simple chromatolysis, and the cell outlines were irregular and ragged and considerable areas of the cells were almost transparent. The remains of the chromatic bodies appeared as a uniform deposit of fine granules, or no traces of them could be found. In badly altered cells the nuclei were almost invariably markedly eccentric or projected beyond the cell border. They were not found to stain diffusely. Yellowish granular pigment was rarely seen in these cells. Many of the Purkinjé cells contained a moderate number of large distinct chromatic bodies, but usually these bodies are thin, ragged, granular, or absent, the deficiency being most marked at the poles and not above the nuclei. In the examination of the brain he found the following general lesions: "The cortical archyochromes showed a bleached chromatic network, though sometimes coarsely granular and indistinct."

These cases by reason of their extreme severity show marked cellular changes comparable in many ways to the lesions observed in the present case. Whether polyneuritis was beginning in these cases it is impossible to say, but the presence of the extreme grades of chromatolysis in the spinal cord throws a somewhat conflicting light on the generally accepted dicta of the process of axonal degenerations. Nor is this question of axonal degeneration made more capable of interpretation when we look at the changes in the cells of the columns of Clarke and the nucleus of Stilling. From a reference to the tabulation of the lesions found in these cells in the present case it will be noted that the cells in this region suffered as much if not more than the anterior horn cells. Such degenerations have before been noted, more particularly in other forms of polyneuritis, and especially have they been the subject of much speculation in Landry's paralysis.

Marchi[1] has shown that, following total ablation of the cerebellum in monkeys, there is a marked degeneration of the direct cerebellar tract and a degeneration of the cells of the columns of Clarke. This degeneration of Clarke's columns is distinctly homologous to the changes in the anterior horn cells following an injury to or the destruction of the peripheral end of the motor neuron. Similar changes have been noted in transverse myelitis, and recently by Barker as a result of epidemic cerebro-spinal meningitis. In this case the direct cerebellar tract was involved and the degeneration of Clarke's column was to be expected. Further we know, however, from the studies of Heilbronner and many others that degenerations of the direct cerebellar tract are found in some cases of alcoholic multiple neuritis. These cases, however, are to be classed, we believe, as fibre degenerations following cell degeneration rather than the reverse, although it must be confessed that we are entirely in the dark with reference to any knowledge of the degree of poisoning that might take place in the terminal arborizations of the direct cerebellar tract in the cerebellum.

But from this point of view, which will explain quite readily the changes observed in Clarke's columns, when the present case is studied and those of many others in which the peripheral sensory neuron is affected by the disease process and a second central neuron bears the impress of that disease, the interpretation is not so clear. Lissauer[2] as early as 1884 noted the degeneration of the cells of the columns of Clarke in tabes, and more recently Marinesco has shown the characteristic picture of an axonal degeneration in a case of tabes and general paresis; the presence of the paresis complicates this case somewhat, yet in this disease, and in others with involvement of the posterior root zone, such typical lesions are found. Sano[3] and a number of others describe similar lesions in Clarke's columns following amputation of a limb, and Sano found lesions also in the motor cortex.

[1] Marchi, V.: "Sull' origine e decorso dei peduncoli cerebellari e sui loro rapporti cogli altri centri nervosi." Rivista Sperimentale di Freniatria, 17, 1889, p. 357.

[2] Lissauer, H.: "Ueber die Veränderungen der Clarkeschen Säulen bei Tabes dorsalis." Fortschritte der Medicin, iv., 1884, p. 113.

[3] Journal de Neurologie et d'Hypnologie.

In Landry's paralysis the cells of this region have been found with similar lesions by a number of writers, and more recently Mills and Spiller[1] have gone over the ground in this disease, and though believing that the entire peripheral sensory neuron may be affected by the disease, this does not explain the lesion in Clarke's columns which are connected only by collaterals with the sensory neuron. Marinesco, in his statement that he believes the changes to be secondary and like those found in polyneuritis, overlooks that the process of degeneration of the anterior horn cell of the motor neuron and those of the cells of the columns of Clarke are not homologous types of degeneration at all. We are unable to offer any explanation why the columns of Clarke should be affected, unless we assume with Van Gehuchten[2] that the ganglion cells in a nervous chain react one upon the other, and that the cutting off of the peripheral sensory stimuli produces a degeneration in the secondary spinal neuron. It is possibly true that both centralists and peripheralists are correct, and that the lesson taught by the changes in these cells in alcoholic neuritis is that the degeneration of the secondary neuron is possible only when in addition to the cutting off of its collateral stimuli the central ganglion cell is overwhelmed by some toxic influence, and yet no such toxic influence can be posited in ordinary nerve sections. With reference, however, to this latter, we might again recur to the fact that perhaps some misinterpretations have been made in estimating the degree of degeneration of the cells of the columns of Clarke. One further point of interest brought out in the present study shows that the disease of the blood-vessels may play a very secondary rôle in the neuritic process. This is quite in opposition to the views held by Fleming, who in two cases was led to the belief that the principal cause of degenerative neuritis was pressure, the result of an inflammatory exudate.[3]

[1] C. K. Mills and W. G. Spiller: "On Landry's Paralysis, with the Report of a Case." Journal of Nervous and Mental Disease, vol. v., 1898, p. 365.

[2] Van Gehuchten: "Le phénomène de chromatolyse consécutif à la lésion pathologique ou expérimentale de l'axone." Bull. de l'Acad. Royale de Belgique, 11, 1897, p. 805.

[3] For a full citation of pathological changes in ganglion cells consult Jelliffe, "Bibliographical Contribution to the Cytology of the Ganglion Cell," Archives of Neurology and Psycho-Patnology, No. 1, 1898, p. 440.

Résumé: From the investigation of the present case the following general conclusions seem warranted:

1. In fatal alcoholic multiple neuritis grave variations from the normal structure (equivalent picture of Nissl) of the ganglion cells of the anterior and posterior horns, the columns of Clarke, the nucleus of Stilling, and the nuclei of the medulla are always to be found when studied by appropriate methods.

2. These cytological variations are characterized by their extreme polymorphism. They may consist of simple swelling of the ganglion cell or of its chromatin particles; fine granular disintegration of the chromatin; destruction of the chromatin; central, peripheral, perinuclear, and general chromatolysis; wandering of the nucleus to an eccentric position, and destruction of the achromatic structures to complete disintegration of the cell.

3. To what extent these lesions are due to the direct action of the alcoholic poison on the molecular structure of the ganglion cell (primary), or the degeneration of the peripheral extensions of both sensory and motor neurons (secondary), cannot, we believe, be accurately determined. The conclusion drawn is, that the peripheral degeneration is the much more important one of the two.

4. The best hypothesis yet offered to account for the degeneration of the cells of the column of Clarke is that of Van Gehuchten, by the assumption that the ganglion cells of a nervous chain exercise the one upon the other a trophic action, the suspension of which produces a chromatolysis and disappearance of the corresponding cells.

Pathological Laboratory,
Columbia University, April, 1899.